REMARKS

I. Preliminary Remarks

A. The Claims

Claims 30-33 are pending in the application. Claims 1-16 were canceled by previous amendments. Claims 17-29 are canceled and claims 31-33 are added by this amendment. For the Examiner's convenience, a list of all claims as they would appear after entry of this amendment is attached hereto as Exhibit A.

Claims 31-33 are added to point out more clearly various embodiments of Applicants' invention. The language in claims 31 describing the "antibody to VCAM-1" closely parallels the language of claim 1 of U.S. Patent No. 5,206,345 (the '345 patent). The present application is a divisional of the application which issued as the '345 patent. Support for claim 31 is found throughout the specification, *e.g.*, at page 4, lines 12-16 and page 17, lines 3-5. The language in claims 32-33 parallels the language of canceled claims 28-29. Support for claims 32-33 is found in the specification, *e.g.*, at page 17, lines 3-33.

B. The Specification

The Examiner noted that the drawings and photographs fail to comply with 37 C.F.R. §1.84, as specified in the form PTO-948 previously mailed with Paper No. 4. The Examiner requested that Applicants amend the Brief Description of the Drawings in accordance with these required changes, particularly those in section 7 (Views). In response, Applicants have amended the specification throughout, including in the Brief Description of the Drawings, to reflect the new numbering of Figures 1, 3, 4, 7, 9 and 11.

The Examiner also objected to an informality in the specification because "BALB/c" is the proper designation of the mouse strain. In response, Applicants have amended the specification to recite "BALB/c."

II. The Claimed Subject Matter

Claims 30-33 relate to methods of using an antibody that binds to vascular cell adhesion molecule-1 (VCAM-1), in the context of Applicants' novel discoveries that bone marrow stromal cells express VCAM-1 and that bone marrow cells, especially those bearing the CD34 antigen, express VLA-4 (the major receptor for VCAM-1). A representative embodiment of such an antibody that binds to VCAM-1 and that possess the ability to block VCAM-1-mediated cell-cell interactions is the 6G10 monoclonal antibody produced by hybridoma ATCC No. HB 10519.

III. The Outstanding Rejections

The Examiner stated that Applicants' arguments with respect to claims 17-18 and claims 19-30 (newly added in the previous amendment) had been considered but were deemed to be moot in view of the new grounds of rejection.

Claims 17-30 were rejected under 35 U.S.C. §101 for lack of utility. It was the Examiner's position that the specification fails to establish the utility of the claimed methods of modulating immune response by VCAM-1-specific agents as a therapeutic regimen in human patients.

Claims 17-30 were rejected and the specification was objected to under 35 U.S.C. §112, first paragraph as assertedly failing to provide an enabling disclosure, for largely the same reasons discussed for the §101 rejection. The Examiner asserted that Applicants had not shown how to use VCAM-1-specific antibodies to modulate the immune response in humans.

Claims 17-30 were rejected under 35 U.S.C. §112, second paragraph as indefinite in the recitation of "modulating" the immune response or the interaction of VCAM-1-expressing cells. Claims 20-29 were also rejected as indefinite due to the recitation of "mAb."

Claims 22-30 were rejected under 35 U.S.C. §102(f) because not all of the authors of Simmons et al. (Blood, 1992) are listed as inventors. Applicants were invited to file a *Katz* declaration.

Claims 17-30 were rejected under 35 U.S.C. §103 as unpatentable over Osborn et al., *Cell,* 59:1203-1211 (1989) (document O29, hereinafter "Osborn"), Elices et al., *Cell,* 60:577-584 (1990) (document O30, hereinafter "Elices"), or Newman et al., U.S. Patent No. 5,011,778 (document A1, hereinafter "Newman"), in view of Graber et al., *J. Immunol.,* 145:819-830 (1990) (hereinafter "Graber"), Rice et al., *Science,* 246:1303-1306 (1989) (document O28, hereinafter "Rice (1989)"), Rice et al., *J. Exp. Med.,* 171:1369-1374 (1990) (hereinafter "Rice (1990)"), Lewinsohn et al., *Blood,* 75:589-595 (1990) (hereinafter "Lewinsohn"), Shimuzu et al., *Immunol. Rev.,* 114:109-143 (1990) (hereinafter "Shimuzu") or Pober et al., *Am. J. Pathol.,* 133:426-433 (1988) (document O14, hereinafter "Pober").

IV. Patentability Arguments

A. The Rejection Under 35 U.S.C. §101 May Properly Be Withdrawn

The Examiner rejected claims 17-30 under 35 U.S.C. §101 as inoperative and therefore lacking utility. It was the Examiner's position that "The specification fails to establish the utility of the claimed methods of modulating immune response by VCAM-specific agents as a therapeutic regimen in human patients." This basis for the rejection is moot in view of Applicants' cancellation of claims drawn to modulating immune response. Applicants address below the Examiner's specific concerns regarding therapeutic utility to the extent that they apply to the remaining claims drawn to methods of modulating interaction between a bone marrow stromal cell and a bone marrow cell by administering an antibody to VCAM-1 in an amount effective to decrease adhesion between the bone marrow stromal cell and the bone marrow cell.

The Examiner stated that:

> Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be

> inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients.

The Board of Patent Appeals and Interferences has held in Ex parte Rubin, 5 USPQ2d 1461, 1462 (Bd. Pat. App. Int. 1987) (quoting In re Langer, 503 F.2d 1380, 183 USPQ 288, 297 (C.C.P.A. 1974)) (emphasis in original) that:

> [A] specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of §101 for the entire claimed subject matter **unless there is reason** for one skilled in the art to question the objective truth of the statement of utility or its scope. [Emphasis in bold added.]

Applicants respectfully submit that the Examiner has not pointed to specific reasons why one skilled in the art would expect anti-VCAM-1 antibodies to be susceptible to inactivation, to be unable to reach the target area, or to cause adverse side effects. Specific reasons are required in view of the fact that others in the art have successfully used monoclonal antibodies to cell adhesion molecules for *in vivo* therapy. For example, Vedder et al., *J. Clin. Invest.*, 81:939-944 (1988) (attached as Exhibit 2 to Applicants' previous amendment and response mailed January 25, 1994) shows that for an anti-CD18 monoclonal antibody that inhibited neutrophil adherence *in vitro*, administration *in vivo* to rabbits improved their survival rate after hemorrhagic shock and resuscitation. As another example, Wegner et al., *Science,* 247:456-459 (1990), attached hereto as Exhibit B, shows that for an anti-ICAM-1 monoclonal antibody that inhibits neutrophil and eosinophil adhesion to endothelium *in vitro*, administration *in vivo* in a monkey model of asthma attenuated eosinophil infiltration into the airways and reduced clinical airway hyperresponsiveness.

The Examiner's statement that:

> Harris et al. [,*TIBTECH, 11*:42-45 (1993),] states that there is widespread acceptance that there is little future for the use of rodent

> monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3) (Tibtech, 1993). Humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies will contain unique amino acid sequences.

is inapplicable to the claims, which do not specify the use of rodent or chimeric antibodies.

The Examiner further stated that:

> In referring to the related adhesion molecule family, Harlan states that whether you go humanized antibody, peptide, soluble receptor or saccharide, it's . . . still a long way to a product that would be appropriate for the clinical setting (Edgington, Biotechnology, 1992; see entire document particularly, page 386, column 3, paragraph 4). Furthermore, Pelletier et al. (J. Immunol., 1992) teach that VCAM-1-specific antibody therapy was not effective in inhibiting allograft rejection in a mouse model (see entire document).

Edgington, *Biotechnology,* 10:385-389 (1992), relates to carbohydrate selectins rather than molecules from the immunoglobulin family such as VCAM-1 or ICAM-1. Pelletier, *J. Immunol.*, 149:2473-2481 (1992) relates to treatment of mice with anti-VCAM-1 antibody to investigate the role of VCAM-1 in the inflammatory response associated with allograft rejection. Any doubts that these references may suggest regarding the use of monoclonal antibody therapy for treating complex, multi-factorial diseases involving leukocyte migration, adhesion and extravasation do not apply in this case. The claimed methods are not drawn to treatment of inflammatory diseases; instead, they simply involve decreasing adhesion of bone marrow cells to bone marrow stromal cells.

Finally, the Examiner stated that:

> Simmons et al. (Blood, 1992) teach that the instant VCAM-1-specific antibody 6G10 did not block the binding of hemopoietic progenitors in vitro (see entire document, particularly page 394, column 1). Therapeutic indices of immunosuppressive drugs can be species- and model-dependent. Applicant has disclosed limited inhibitory data by the VCAM-specific antibody 6G10 under defined in vitro conditions. Applicant has not provided any evidence a priori that establishes the efficacy of the claimed invention for the treatment of human disease. Therefore it does not appear that the asserted utility of the claimed method for treating humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. See MPEP 608.01 (p),

Applicants respectfully disagree with the Examiner's characterization of Simmons et al., *Blood,* 80:388-395 (1992) (hereinafter "Simmons"). The cited portion of Simmons merely states that 6G10 antibody did not "*completely* block the binding of hematopoietic progenitors (emphasis added)." Simmons reports the effect of 6G10 monoclonal antibody on adhesion of *human* bone marrow cells to stroma. The experimental data in Simmons shows that 6G10 was 90% effective in inhibiting adhesion of human stem cells and progenitor cells:

> **6G10 inhibited the adhesion of both classes of progenitors [granulocyte-macrophage colony-forming cells (CFU-GM) and erythroid progenitors (BFU-E)] to cytokine-treated stromal cells by up to 90%** relative to that seen with isotype-matched control MoAbs [monoclonal antibodies]. Significantly, **6G10 also effectively blocked binding of progenitors to uninduced stromal cells**, suggesting constitutive expression of VCAM-1 by components of the adherent cell layer. . . [Emphasis added.]
> Simmons at page 390, second column.

Simmons also demonstrated that 6G10 inhibited adhesion to bone marrow stroma of human primitive hematopoietic progenitors with the capacity to initiate and sustain hematopoiesis. See Simmons at page 392, first column. Simmons thus confirms that the utility disclosed in the specification is in fact believable to persons of skill in the art.

For the foregoing reasons, the disclosed utility of claims 30-33 is believable to persons of skill in the art, and the rejection under 35 U.S.C. §101 may properly be withdrawn.

B. The Rejection Under 35 U.S.C. §112, First Paragraph May Properly Be Withdrawn

The Examiner rejected claims 17-30 and objected to the specification for failure to provide an enabling disclosure. The Examiner stated that:

> A) Applicant has not disclosed how to use VCAM-specific antibodies therapeutically in humans. There is insufficient written description of the invention with respect to the in vivo operability of VCAM-specific antibodies to use applicant's invention for the reasons discussed in detail in the previous rejection made under 35 U.S.C. § 101 (see paragraph 20). Although the VCAM-specific antibody 6G10 was able to inhibit lymphocyte binding under defined in vitro conditions, no examples have appeared in the application for predicting VCAM-specific immunotherapy for human diseases. Therefore it does not appear that the asserted operability of the claimed method and compositions for modulating immune responses in humans would be believable prima facie to persons of skill in the art in view of the contemporary knowledge in the art. It appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teaching of the specification alone.
>
> B) It is unclear from the specification whether any VCAM-specific binding agent can modulate the immune response in vivo. Applicant has exemplified some in vitro inhibition of lymphocyte binding under defined conditions with the VCAM-specific antibody 6G10. As indicated above in section 20, Harlan states that whether you go humanized antibody, peptide, soluble receptor or saccharide, it's still a long way to a product that would be appropriate for the clinical setting as it applies to adhesion molecules (Edgington, Biotechnology, 1992; see entire document particularly, page 386, column 3, paragraph 4). Furthermore, Pelletier et al. (J. Immunol., 1992) teach that VCAM-1-specific antibody therapy was not effective in inhibiting allograft rejection in a mouse model (see entire document). Simmons et al. (Blood, 1992) teach that the instant VCAM-1-specific antibody 6G10 did not block the binding of hemopoietic progenitors in vitro (see entire document, particularly page 394, column 1). Therapeutic indices of immunosuppressive drugs can be species- and model-dependent. There is no evidence relating to the inhibition by any agent that binds VCAM to enable all of the agents embraced by the claims.

The Examiner's reasons supporting this rejection are essentially the same as the reasons supporting the rejection under 35 U.S.C. §101, and have been addressed above in section A.

The Examiner further stated that:

> The disclosure is not enabled for modulating the immune response with any VCAM-binding agent, all of which are embraced by the claims. Compositions comprising any agent that binds VCAM do not necessarily correlate with their ability to modulate immune response in vivo. Applicant has not set forth the metes and bounds of these VCAM-specific binding agents. The specification has not provided

> sufficient direction or guidance to one of skill in the art to properly select or administer any VCAM-binding agent that are required to practice the broadly claimed methods. It appears that undue experimentation would be required of one skilled in the art to practice the broadly claimed methods and their respective compositions using the teaching of the specification alone.

The Examiner's comments regarding modulating the immune response are moot in view of the cancellation of the claims drawn to methods for modulating immune response. With respect to the remaining claims drawn to methods of modulating interaction between bone marrow cells and stroma, Applicants have amended claim 30 to recite "antibodies to VCAM-1" rather than agents that specifically bind VCAM-1. The use of antibodies to VCAM-1 is enabled in the specification, which describes, *e.g.* at page 15, lines 19-34 and page 21, lines 13-17, the use of monoclonal antibody to inhibit VCAM-1-mediated cell-cell adhesion. In addition, claim 30 as amended more clearly sets forth the metes and bounds of Applicants' invention.

Applicants respectfully disagree with the Examiner that undue experimentation would be required of one skilled in the art to practice the claimed methods. Vedder and Wegner show that those of ordinary skill in the art are readily able to determine effective dosages of monoclonal antibodies for *in vivo* administration, drawing on knowledge obtained from *in vitro* studies. In this case, as in *Ex parte Skuballa*, 12 USPQ2d 1570, 1571 (Bd. Pat. App. Int. 1989),

> **the skilled worker in this art could readily optimize effective dosages and administration regimens** for each of the recited utilities. As is well known, the specific dosage for a given patient under specific conditions and for a specific disease will routinely vary, but **determination of the optimum amount in each case can readily be accomplished by simple routine procedures**. [Emphasis added.]

Finally, the Examiner stated that:

> C) It is not clear from the specification whether 6G10-recognized molecules immunoprecipitated from TNF/IL-4 activated cultured human bone marrow stroma differ from VCAM (see specification, page 17, paragraph 1). These species include one with a molecular weight of 115-130 kD while the other was larger than 200 kD, as compared to the 100 kD of traditional VCAM-1 antigens recognized. Is the 115-130 kD species the seven domain (vs. six domain) VCAM structure? Is there any evidence of this? What is the greater than 200 kD structure?

> It appears that this antibody binds molecules other than the art-recognized VCAM. Therefore, the disclosure is not enabling for the antibody 6G10 to bind VCAM exclusively. Applicant has not set forth the metes and bounds of the target specificity of the 6G10 antibody, which was used to enable the instant invention. Therefore, it remains unclear whether the effects of 6G10 [are] mediated through VCAM alone or through multiple molecular species. The specification has not provided sufficient guidance to the specificity of the 6G10 antibody to enable the claimed invention's specificity for VCAM alone.

The Examiner's focus on 6G10 is misplaced; Applicants' novel discoveries are that bone marrow stromal cells express VCAM-1 and that bone marrow cells, especially those bearing the CD34 antigen, express VLA-4 (the major receptor for VCAM-1). The identification of VCAM-1 on bone marrow stromal cells provides guidance for using antibodies that bind specifically to VCAM-1. In addition, the identification of the VCAM-1-receptor VLA-4 (also known as $\alpha 4$-$\beta 1$) on bone marrow cells confirms the desired target specificity to VCAM-1.

In any case, the specification does show the VCAM-1-specificity of 6G10 monoclonal antibody. For example, at page 15, lines 29-34 the specification states that 6G10 monoclonal antibody binds specifically to transfectants expressing VCAM-1. No reactivity was observed with the other ELAM-1 or ICAM-1 transfectants.

C. The Rejection Under 35 U.S.C. §112, Second Paragraph May Properly Be Withdrawn

Claims 17-30 were rejected under 35 U.S.C. § 112, first and second paragraph for indefiniteness and nonenablement in the recitation of "modulating" the immune response or the interaction of VCAM-1-expressing cells. It was the Examiner's position that the characteristics of "modulating" are unknown because "[m]odulation can occur either as stimulation or inhibition, for example." It was also the Examiner's position that Applicants have only enabled inhibition, not stimulation.

The issue of indefiniteness with regard to modulating the immune response is moot due to cancellation of claims drawn to those methods. Applicants respectfully submit that the characteristics of the modulation involved in claims 30-33 are evident from those

claims' recitation of administration "in an amount effective to decrease adhesion" and that the specification enables this type of modulation.

The Examiner also deemed claims 20-29 to be indefinite in the recitation of "mAb." This rejection is mooted by the cancellation of those claims, and it does not apply to claims 30-33, which do not recite "mAb."

C. The Rejection Under 35 U.S.C. §102(f) May Properly Be Withdrawn

Claims 22-30 were rejected under 35 U.S.C. § 102(f) on the asserted ground that Applicants did not invent the claimed subject matter, because not all of the authors of Simmons et al. (Blood, 1992) are listed as inventors. It was the Examiner's position that:

> The claimed modulation of VCAM-expressing cells by the 6G10 antibody as described in the instant application are cited in Simmons et al. (Blood, 1992). This reference presents an ambiguity with regard to inventorship because the named authors include[] Longenecker, Berenson, Torok-Storb, who are not listed as inventors herein. This reference is written as "we show". This reference says nothing about inventorship. Because of this ambiguity, it is incumbent on applicants to provide a satisfactory showing which would lead to a reasonable conclusion that applicants alone are the inventors of the claimed invention. See In re Katz, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). To resolve the ambiguity, applicants may file declarations by the non-applicant co-authors of the references disclaiming the invention or a declaration by applicant setting forth the facts which provide an explanation as to why the non-applicant co-authors are not inventors.

The Examiner's rejection is fully addressed by the submission herewith of the Declaration of Boris Masinovsky, a co-inventor of the instant application attached hereto as Exhibit C. As required by In re Katz, 687 F.2d 450, 215 USPQ 14 (CCPA 1982), Dr. Masinovsky in his declaration states that Longenecker, Berenson and Torok-Storb were not involved in the conception or reduction to practice of the subject matter of the instant application, and made no inventive contribution.

D. The Rejection Under 35 U.S.C. §103 May Properly Be Withdrawn

Claims 17-30 were rejected under 35 U.S.C. § 103 as unpatentable over Osborn, Elices or Newman in view of Graber, Rice (1989), Rice (1990), Lewinsohn, Shimizu or Pober. The Examiner characterized the first three references as follows:

> Claims 17-30 are drawn to the modulations of VLA-VCAM cell interactions by VCAM-specific binding agents. Osborn et al. teach the expression of VCAM and its role as a cell adhesion molecule in normal tissue development and inflammatory conditions (see entire document). Osborn et al. also teach that VCAM-specific antibodies can block VLA-mediated binding and relate to this inflammatory response[] (see page 1208, column 2). Osborn et al. also teaches that VCAM-dependent pathways would provide intervention points for correction of pathologies associated with acute and chronic inflammation. Elices et al. extend these observations to indicate that VLA-4 on leukocytes interacts with VCAM on endothelial cells and this can be block[ed] by antibodies (see entire document). Similarly, Elices et al. relate this interaction to normal and disease states involving leukocytes and their adhesion and recruitment. Newman et al. teach the use of 1E7/2G7-specific antibodies to inhibit leukocyte inflammatory responses (see entire document). As Graber et al. teaches, the 1E7/2G7 antigen is VCAM (see page 829, Note Added in Proof). Graber et al. is provided to indicate the 1E7/2G7 was VCAM and not to serve as prior art per se. These references differ from the claimed invention by not describing the 6G10 antibody or IL-4 activation per se. However, the specificity of the claimed intervention is VCAM and it would not have [been] critical to the targeting [of] the VCAM adhesion molecule that was activated through IL-4 or through other stimulants.

The Examiner characterized the remaining references as follows:

> Rice et al. (Science, 1989) teach the expression of INCAM-110 (VCAM) on endothelial cells and dendritic cells (see page 1305, column 1). Rice et al. (J. Exp. Med., 1990) extends this observation to localize INCAM-110 (VCAM) expression at inflammatory sites and on dendritic cells as well as its role in lymphocyte adhesion and activation (see entire document, particularly, page 1372, paragraph 3). Lewinsohn et al. teach the expression of adhesion molecules on human hemopoietic progenitor $CD34^+$ cells and draws attention to MEL-14, the murine analog of VLA (see entire document, particularly page 594). Shimuzu et al. review the art-known role of VLA-4 in T cell adhesion and stimulation and the identification of its ligand VCAM (see entire document, particularly pages 132-137 and Note Added in Proof). Prober et al. teach the art-known role of adhesion molecules in leukocyte adhesion and activation and the targeting of such interactions in manipulating pathologic diseases (see entire document).

However, ***none*** **of the cited references identifies the expression of VCAM-1 on bone marrow stromal cells.** In Osborn and Newman, the investigators did not test for

the presence of VCAM-1 (or 1E7/2G7 antigen) on bone marrow stromal cells. Elices reports that VLA-4 is the ligand for VCAM-1, but does not identify VCAM-1 on bone marrow stromal cells or VLA-4 on bone marrow stroma. In Rice (1989) and Rice (1990), both of which relate to INCAM-110 (now known as VCAM-1), the investigators did not find (or did not test for) expression of VCAM-1 on bone marrow stroma. Lewinsohn reports on the expression of H-CAM (CD44) on hematopoietic progenitor cells in bone marrow. Lewinsohn *does not suggest* that VLA is expressed on hematopoietic progenitor $CD34^+$ cells.[1] The Examiner is mistaken in stating that MEL-14 is the murine analog of VLA; rather, the MEL-14 antigen is an L-selectin. See *Adhesion: Its Role in Inflammatory Disease*, Harlan and Liu eds., W.H. Freeman and Company (1992) at page 129, attached hereto as Exhibit D. Shimuzu, which reviews the role of integrins on T-cells, does not relate to bone marrow cells or bone marrow stroma. Pober discusses the role of adhesion molecules in activation of vascular endothelium and does not discuss bone marrow cells or bone marrow stroma.

The Examiner's position is that:

> Therefore, the art recognized the role of interfering [with] adhesion interactions to modulate immune responses, including through VLA/VCAM pathways. VCAM was known to be present on endothelial cells and dendritic cells, both intimately involved in T cell adhesion and activation. VCAM's ligand VLA was known to be associated with either T cells or bone marrow precursors. The art teaches the generation[] of VCAM-specific reagents as taught by Osborn, et al., Elices et al. and Newman et al.; therefore the skilled artisan would have derived the claimed 6G10 antibody of the instant claims by routine experimentation. The skilled artisan would have use[d] such VCAM-specific reagents to inhibit lymphocyte or hemopoietic interactions with VCAM-expressing cells to condition patients for various inflammatory conditions or hemopoietic reconstitution. One of ordinary skill in the art at the time the invention was made would have been motivated to select and evaluate the efficacy of VCAM-specific agents in a therapeutic regimen to modulate

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[1] In any case, a disclosure of the presence of VLA-4 on bone marrow cells would not teach the ordinary skilled artisan that bone marrow cell adhesion to stroma is mediated by VCAM-1/VLA-4 interactions, because VLA-4 binds not only to VCAM-1 but also to fibronectin. Fibronectin is a well-documented component of the extracellular matrix that is synthesized by bone marrow stromal cells (Simmons at page 390, first column), and the existence and function of VLA-4 on bone marrow cells could be explained by its interaction with fibronectin.